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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/148,234	09/04/1998	IOANNIS MOUTSATSOS	P-4739-US	3002

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/148,234	MOUTSATSOS ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28* is/are rejected.

7)☒ Claim(s) *24 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-23 have been cancelled. Claim 24 has been amended.

Claims 24-28 are pending and under examination.

2. Applicant states that, in the telephone conversation that took place on November 5, 2007, the Examiner indicated that claims reciting MSCs administration in the absence of a matrix to promote organized bone formation would be novel, unobvious, and supported by the specification and the examples provided by the specification. This statement is incorrect. During the telephone conversation, Applicant was only informed that amending the claims to recite administration in the absence of a supporting matrix would obviate the obviousness-type rejection because the cited references do not teach administering MSCs in the absence of a support matrix. Applicant was also advised that such an amendment to the claims could introduce new matter. At no point did the Examiner indicate that claims reciting administration without a support are novel and unobvious or that such claims are supported by the specification.

Response to Arguments

Claim Objections

3. Claim 24 and 27 remain objected to because of the recitation of "bone morphogenenetic protein" and of "bone morphogenesis protein". Appropriate correction to "bone morphogenic protein" is required.

Specification

4. The objection to the disclosure is withdrawn in response to Applicant's amendment filed on 12/17/2007.

Claim Rejections - 35 USC § 103

5. The rejection of claims 24-28 under 35 U.S.C. 103(a) as being unpatentable over Bruder et al. (J Cell Biochem, 1994, 56: 283-294), in view of Bonadio et al. (U.S. Patent No. 5,763,416) is withdrawn in response to Applicant's amendment to claim 24 filed on 12/17/2007.

New Rejections

Claim Rejections - 35 USC § 112, new matter

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 24-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 2, 8-9, 11, 14-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the amendment to the claim to recite implanting transformed MSCs “in the absence of an exogenously supplied matrix” is considered new matter.

Applicant points to Examples 8 and 11 for support, wherein, according to Applicant, there is a teaching of MSCs implantation in the absence of a collagen sponge support. It is noted that the indicated Examples recite implantation in collagen sponges (see Example 8, p. 6, lines 7-11, wherein, although there is no direct disclosure of MSCs in a collagen sponge, the recitation of a control consisting of collagen sponge only is indicative that the MSCs cells are transplanted with a collagen sponge as a carrier, otherwise the use of a control consisting only of a collagen sponge would not be adequate; Example 11, p. 21, lines 10-28). A search of the remaining portions of the specification failed to provide literal support for implanting MSCs without a matrix.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02

teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claim Rejections - 35 USC § 112, enablement

8. Claims 24-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of

the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The instant claims are drawn to a method of inducing organized, functional bone formation by implanting genetically engineered MSCs in the absence of a supporting matrix. However, neither the instant specification nor the art is enabling for the present claimed invention for the reasons discussed below.

Bone formation cannot occur by simply implanting MSCs in the absence of a support matrix. The art clearly teaches that organized, functional bone formation requires retaining the cells and the factors secreted by the cells for a sufficient time to promote repair, which can be accomplish only by using a support matrix. For example, Bruder et al. (J Cell Biochem, 1994, 56: 283-294, of record) teach:

> "In order to effect osseous repair in a local defect, the cells must be delivered to the site in an appropriate carrier. We envision the ideal vehicle as biocompatible to minimize inflammation, osteoconductive to foster integration, resorbable to promote its own replacement, supportive of mesenchymal stem cell attachment and porous to facilitate rapid vascularization. In many ways, this vehicle would functionally resemble hypertrophic cartilage of the growth plate or fracture callus".

Along the same lines, Leach et al. (Expert Opin Biol Theor, 2004, 4: 1015-1027) teach:

> "Transplantation of bone-forming cells to a repair site can promote can promote bone regeneration by direct participation of these cells in bone formation and by the release of osteoinductive factors by these cells.

> The infusion or injection of transplanted cells is limited due to their potential to migrate away from the repair site, apoptosis or necrosis. Physical association with carriers in various forms has proven to be an effective means for maintaining bioactive factors and cells at the desired location for prolonged time."

Additionally, the instant specification fails to provide sufficient guidance for a skillet artisan on how to perform the claimed method in the absence of a support matrix; there is not teaching that organized, functional bone formation can occur by implanting cells without a matrix. It is noted that all the examples provided by the specification teach the use of collagen sponges.

Based on the teachings in the art and the lack of guidance in the specification, one of skill in the art would not recognize that implanting MSCs in the absence of a support would lead to organized, functional bone formation as claimed. In conclusion, it is considered that the invention, as presently claimed is not enabled.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

/Joseph T. Woitach/
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